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Mortality effect of higher versus lower blood pressure targets in vasodilatory shock: an updated systematic review and meta-analysis

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Title:

Mortality Effect Of Higher Versus Lower Blood Pressure Targets In Vasodilatory Shock: An Updated Systematic Review And Meta-Analysis

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Abstract

Objective: To determine the impact of higher versus lower mean arterial pressure (MAP) targets on mortality and other outcomes in patients with vasodilatory shock.

Design: A systematic review and meta-analysis of randomised controlled trials (RCTs) following PRISMA guidelines with the protocol preregistered with PROSPERO (CRD420251087844).

Data Sources: PubMed, Embase, CENTRAL, and Scopus from their inception until July 2025.

Methods: This review included RCTs that compared a higher MAP target arm, typically 80±5 mmHg or the physiologically higher target arm within the trial, to a lower target arm (generally 65±5 mmHg) in adult patients with vasodilatory shock. The primary outcome was all-cause mortality. The analysis utilised random-effects models, subgroup analyses, and Bayesian methods.

Results: Four RCTs with a total of 3,873 patients were included. A higher MAP target was associated with a 10% increase in 28-day mortality (RR 1.10, 95% CI 1.01–1.19; P=0.03). A similar trend toward increased 90-day mortality was observed, with a risk ratio of 1.10 (95% CI 1.00–1.22; P=0.05). Subgroup analyses revealed no benefit from higher targets for any patient group, including those with advanced age or chronic hypertension. A higher MAP target was also linked to fewer RRT-free days (mean difference -1.64, 95% CI -3.05 to -0.23; P = 0.02) and a greater risk of arrhythmia (RR 1.32, 95% CI 1.01–1.72; P=0.04). The Bayesian analysis corroborated these findings, revealing a high posterior probability of harm (97.8% for 28-day mortality and 98.7% for 90-day mortality).

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Conclusions: In patients with vasodilatory shock, universal high MAP targets are associated with increased mortality compared with lower targets, with moderate certainty. These results should encourage the adoption of lower MAP targets and highlight the importance of avoiding the potential harm associated with excessive vasopressor use. Future research should focus on individualised blood pressure rather than fixed targets.

Introduction

Maintaining an adequate mean arterial pressure (MAP) is fundamental for organ and tissue perfusion in vasodilatory shock. The optimal use of vasopressors requires consideration of a careful balance between increasing perfusion pressure against vasopressor toxicity.[1] While current international guidelines recommend an initial MAP target of 65 mmHg[2], most of the available evidence supporting this threshold comes from retrospective cohorts.

Nevertheless, clinical practice frequently surpasses these guideline recommendations. In a recent cohort, among patients with septic shock receiving vasoactive support, only 20% had a mean MAP below 70 mmHg, while 9% had a MAP in excess of 80mmHg.[3] This may reflect a perception of increased risks associated with low MAPs and relative safety of higher values. For example, Maheshwari et al.[4] reported that for every one unit increase in the time-weighted average MAP below 65 mmHg increased the odds of in-hospital death by 11% (95% CI 7.8–15.1%). Similarly, Vincent et al.[5] noted that even short periods of MAP below 65 mmHg were associated with increased ICU (Intensive Care Unit) mortality. Whether aiming for higher MAP targets (≥75–80 mmHg) might improve outcomes, especially in subgroups such as patients with chronic hypertension or elderly individuals, remains to be elucidated.

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Previous randomised controlled trials (RCTs) and meta-analyses have not conclusively supported the superiority or harm associated with higher MAP targets. The SEPSISPAM[6] trial reported no overall mortality benefit with a higher MAP target (80–85 mmHg) but signalled potential renal protection in patients with chronic hypertension. Similarly, the 65 trial[7] revealed no difference in mortality between patients with a MAP target of 60–65 mmHg and those receiving usual care. Subsequent meta-analyses[8,9] have faced limitations due to heterogeneity in patient populations, a focus on short-term mortality, and insufficient power to observe meaningful differences in key subgroups. Therefore, gaps in knowledge remain, including the effects of higher MAP targets on long-term mortality (e.g., 90 days), differential impacts in elderly patients (≥65 years), those with preexisting chronic hypertension, and safety outcomes such as arrhythmias or the need for renal replacement therapy (RRT).

An individual-patient data meta-analysis[10] (n=3352 patients) published in 2024 reported a risk ratio of 0.93 (95% Credible Interval [CI] 0.76--1.07; low certainty, posterior probability of benefit 87%) concerning 90-day all-cause mortality for a lower MAP target. Crucially, elevated pressure targets were not found to benefit any of the analysed subgroups of patients. Since then, the OPTPRESS (2025)[11] trial has signalled harm from higher MAP targets, adding further data that potentially provides more power and granularity, including to analyse subgroup and secondary outcomes.

We therefore conducted an updated systematic review and meta-analysis of RCTs comparing a higher MAP target arm to a lower target arm in adult patients with vasodilatory shock. Our primary goal was to determine their association with 28-day and 90-day all-cause mortality, including in predefined subgroups. Renal outcomes and safety profiles were subsequently assessed. This updated review

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aims to clarify the effect of higher versus lower pressure targets in vasodilatory shock and guide haemodynamic management based on the best recent evidence.

Methods

This systematic review and meta-analysis were conducted according to a preregistered protocol (PROSPERO: CRD420251087844). It aimed to address the following clinical research question: What is the impact of targeting a higher mean arterial pressure (MAP) compared to a lower MAP on all-cause mortality in patients with vasodilatory shock? The population studied included adult patients (≥18 years) with vasodilatory shock requiring vasopressor support. The intervention assessed was haemodynamic management strategy targeting a higher MAP (typically ≥75–80 mmHg or the physiologically higher target arm within the trial) with the comparator being a management strategy targeting a lower MAP (typically 60–65 mmHg). The primary outcome assessed was all-cause mortality at 28 and 90 days, if reported. Moreover, data for secondary renal outcomes (Days alive and free from renal replacement therapy at 28 days [RRT-free days], and overall RRT-use) and secondary adverse reactions (e.g., arrhythmias) was extracted and analysed, if reported.

Identification of records:

We conducted a systematic search to identify all randomised controlled trials (RCTs) comparing higher versus lower MAP targets in the defined population. The search was performed in the following electronic bibliographic databases from their inception until 31st July 2025: PubMed/MEDLINE, Embase, Cochrane Central Register of Controlled Trials (CENTRAL), and Scopus. The search strategy used a combination of Medical Subject Headings (MeSH) and keywords related to “blood pressure,” “mean arterial pressure,” “MAP target,” “intensive care,” “shock,” and

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"randomized controlled trial". No restrictions were applied based on publication date. The review was limited to studies published in the English language. References of included articles and relevant reviews were also screened for additional studies. Full database search strings and PRISMA materials are in Supplement S1.

Studies were excluded if they involved paediatric or obstetric populations, patients with shock of primary aetiologies other than vasodilatory (e.g., haemorrhagic), or were non-randomised studies, trial protocols, or conference abstracts without a full-text publication.

Study selection and data extraction:

The study selection process followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.[12] Search results were imported into a reference management software, and duplicates were removed. Titles and abstracts were screened independently by two reviewers against the eligibility criteria. The full texts of potentially relevant records were retrieved and assessed independently by the same two reviewers. Any disagreements regarding inclusion were resolved through discussion or, if necessary, by consulting a third reviewer. The study selection process was documented using a PRISMA flow diagram.

Data were extracted independently by two reviewers using a standardised, piloted data extraction form. The following information was extracted from each included study: first author, year of publication, country, study design, patient population characteristics, inclusion and exclusion criteria, sample size, specific MAP targets for intervention and comparator groups, details of vasopressor management, and outcome data. The primary outcome extracted was all-cause mortality at 28 days and 90 days, if reported. Data on secondary outcomes, including renal outcomes

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(RRT-free days, and RRT-use) and safety outcomes (e.g., arrhythmias), were also extracted where available. Authors of the primary studies were not contacted for additional information.

Assessment of risk of bias in included studies:

Two authors independently assessed the risk of bias for each included RCT using the Cochrane Risk of Bias tool for randomised trials (RoB 2.0).[13] The tool was applied across the following domains: bias arising from the randomisation process, bias due to deviations from intended interventions, bias due to missing outcome data, bias in the measurement of the outcome, and bias in the selection of the reported result. Judgements for each domain were categorised as "low risk," "some concerns," or "high risk." Disagreements between reviewers were resolved by consensus. Moreover, they assessed the overall quality of evidence at the outcome level according to the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) system.[14]

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Data synthesis and statistical analysis:

Data synthesis and analysis were performed as per the pre-registered protocol (PROSPERO CRD420251087844). Dichotomous outcome data (mortality, need for RRT) are presented as risk ratios (RR) with 95% confidence intervals (CIs). Continuous outcome data (RRT-free days) are presented as mean differences (MD) with 95% CIs.

All analyses were performed using a random-effects model with the Mantel–Haenszel method due to anticipated clinical heterogeneity. Restricted maximum likelihood was used as the between-study heterogeneity estimator.

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Statistical heterogeneity was assessed using the I^2 statistic, where I^2 values of 25%, 50%, and 75% were considered to represent low, moderate, and high heterogeneity, respectively.

Meta-analyses were conducted via the 'metafor' package (R, version 4.5.1, R Foundation for Statistical Computing) and Cochrane Review Manager 5.4 (RevMan). Continuity corrections were applied where necessary. Subgroup interactions were tested via Wald statistics. Trial sequential analysis was performed to assess the accrued information size via a web-based platform.[15]

Pre-specified subgroup analyses were performed for the primary outcome based on patient age (<65 vs. ≥65 years), presence of chronic hypertension, and septic shock aetiology. The credibility of subgroup effects was assessed using the Instrument to assess the Credibility of Effect Modification Analyses (ICEMAN).[16] This tool evaluates whether subgroup hypotheses are prespecified, biologically plausible, supported by prior evidence, statistically robust (interaction test), consistent across related outcomes, and free from bias. Sensitivity analyses were also planned to assess the robustness of the findings by excluding studies with a higher risk of bias or with substantial design differences.

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Bayesian analysis:

Although the primary frequentist analysis was pre-specified in the PROSPERO protocol, we complemented it with a Bayesian hierarchical meta-analysis—a decision made prior to any data extraction or synthesis—to enhance the robustness and clinical interpretability of our findings. This was a planned methodological enhancement, adopted because Bayesian methods offer distinct advantages for evidence synthesis.[17] Specifically, this framework allows for the direct quantification of the probability of benefit or harm (via posterior

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probabilities), a critical feature for clinical decision-making.[18] Furthermore, it provides more stable inference for effect estimates, particularly those near the null or of borderline statistical significance[19], and ensures transparent evaluation of the conclusions' fidelity using varying priors.[20]

A Bayesian hierarchical meta-analysis was performed in R (version 4.5.1) via *brms* (version 2.22.0) with the *cmdstanr* backend. Outcomes were modelled with a binomial likelihood and logit link, including random intercepts and treatment effects by trial. The primary prior for the pooled log-odds ratio was normal (0, 1.5); an alternative prior was a sceptical normal (0, 0.10); a fixed-effects model and leave-one-out trial exclusions were used for sensitivity analysis. Between-trial SDs used half-Student-t (3, 0, 1) priors and correlations an LKJ (2) prior. Posterior draws were summarised as median risk ratios (RRs) with 95% credible intervals via posterior marginal standardisation, and we reported the posterior probability of harm (RR > 1), abbreviated as P(RR>1). The model was fit with the Hamiltonian Monte Carlo method (4 chains, 20,000 iterations), assessed for convergence and fit with standard diagnostics and posterior predictive checks. Given the predicted small k, we report τ with 95% CrIs and 95% prediction intervals on the RR scale via posterior marginal standardisation. The full prior rationale, endpoint-specific tuning parameters, diagnostics, and R code are provided in the Supplementary Appendix 1: Bayesian analysis.

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Results

Literature search:

Figure 1 presents the PRISMA flow diagram outlining the study selection process. Our initial search of electronic databases yielded 3930 records. After removing 470 duplicate entries, we screened the remaining records based on titles and abstracts, and excluded 3430 that were irrelevant. We subsequently evaluated 30 full-text

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articles for eligibility and included four RCTs[6,7,11,21] in the primary quantitative analysis. Notably, a fifth identified RCT[22] was excluded from the primary analysis because of the unique pathophysiology and haemodynamic profile of its cirrhotic patients, which substantially limits comparability with the other included trials. However, it was included in the sensitivity analysis to ensure the robustness of our findings.

Study characteristics:

Table 1 summarises the characteristics of the identified studies. With the aforementioned exception of the TARGET-C trial[22], the remaining four were included in the primary analysis, having enrolled 3,873 adult patients from Canada, Japan, France, the United Kingdom, and the United States. Definitions of lower and higher MAP targets varied across studies. In all trials, septic shock was the most common cause of vasodilatory shock. Although the achieved MAP was significantly lower in the lower MAP group than in the higher MAP group, the values in the lower MAP group still exceeded their predefined targets. Noradrenaline was the most frequently used vasopressor and was administered for a longer duration in the higher MAP target group. The OPTPRESS[11] trial was the only study with a protocolised use of vasopressin. No significant differences were observed in fluid administration, steroid use, or urine output between the groups when reported.

Figure 1: PRISMA flow diagram

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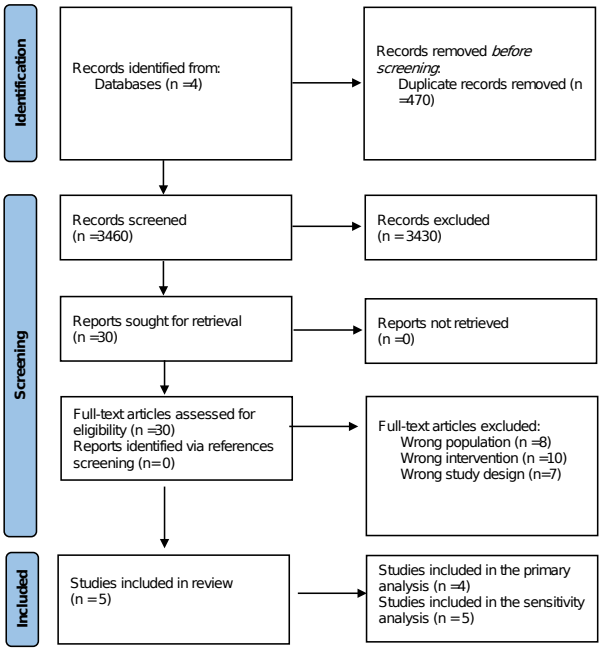

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Table 1: Characteristics of the identified Randomised Clinical Trials.

Characteristic / Trial	SEPSISPAM (NEJM 2014)	OVATION (ICM 2016)	65 Trial (JAMA 2020)	TARGET-C (2023)*	OPTPRESS (ICM 2025)
Setting	Multicenter (France)	Multicenter (Canada and USA)	Multicenter (UK)	Single center (India)	Multicenter (Japan)
Number of ICUs involved	29	11	65	1	29
Sample size (N)	776	118	2463	150	516
Primary outcome	28-day mortality	Hospital mortality	90-day mortality	28-day mortality	90-day mortality
Inclusion criteria	Septic shock <6h; NE ≥0.1 µg/kg/min.	Vasodilatory shock; vasopressor requirement expected≥6h.	Age ≥65; vasodilatory shock; vasopressor requirement expected ≥6h; NE ≥0.1 µg/kg/min.	**Known cirrhosis** + Septic shock defined by persisting hypotension requiring NE>0.01 µg/kg/min and arterial lactate >2 mmol/L, despite adequate volume resuscitation.	Septic shock per SEPSIS-3 criteria; Age ≥65; NE started <3h.
Exclusion criteria	Pregnancy; DNR; legal constraints.	NE ≥24h; imminent death <48h; other shock types.	Other types of shock; hypotension solely due to post-cardiopulmonary bypass vasoplegia; CNS/Spinal injury; death perceived as imminent.	Age <18 years, severe known cardiopulmonary disease, pregnant patients, with chronic heart and lung diseases, expected life expectancy <24 h, "refractory shock".	NE ≥3h before randomization; cardiac arrest prior to enrollment, treatment limitation orders.
Lower MAP target (mmHg)	65–70	60–65	60–65	60-65	65–70
Higher MAP target (mmHg)	80–85	75–80	Usual care: median 72–73 mmHg (IQR 70.1–80.8)	80-85	80–85
Intervention duration	5 days or until vasopressor discontinuation	Until ICU discharge (median 3 days)	Until ICU discharge (median 4 days)	Until the reversal of shock, day 5 or the development of adverse	72 hours (protocol-defined)
Actual MAP Separation (mmHg)	15	9	6	8[#]	5[¶]
Excess Noradrenaline use in the higher-MAP target arm	110%[§]	40%	49%	35%[††]	62%
Excess vasopressor duration in the higher-MAP target arm	27%	66%	15%	Not reported/assessable	54%
Mean Age (years ±SD)	Low: 65 ±15 High: 65 ±13	Low: 66 ±13 High: 63 ±13	Low: 75.2 ±7.0 High: 74.8 ±7.1	Low: 46.7 ±9.1 High:45.0 ±12.9	Low: 76.3 ±7.6 High: 76.7 ±7.8
%Age ≥65	53%	55%	100%	<5%[‡]	100%
%Septic shock	100%	70%	48% (SEPSIS-3 criteria)	100% (as per inclusion criteria)	100% (SEPSIS-3 criteria)
%Chronic hypertension	44%	45%	46%	9%	53%

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Footnote: The sample size refers to the number of patients with reported mortality outcomes (e.g., the JAMA-65 trial, in which 2600 patients were randomised, but the primary outcome was available for 2463 patients). Abbreviations: NE = noradrenaline use; DNR = do not resuscitate orders; CNS = central nervous system. *Excluded from primary analysis (see sensitivity analysis). †Estimated from reported mean and standard deviation. §Estimated using the Population-Average Daily Exposure method by multiplying the percentage of patients receiving norepinephrine by the median dose (µg/kg/min) among those recipients, aggregated across the four days, using data from the article's Table S2A. # Estimated from article's Fig. 2A by averaging the mean differences between high- and low-target groups across all available time points (0 h–5 days, range 6–12 mmHg) during the intervention period in the intention-to-treat population. ††Estimated from article's Fig. 2B by calculating the mean proportional difference between high- and low-target groups across all available time points (0 h–5 days) during the intervention period, using [(High − Low)/Low] × 100, with mean infusion rates (µg/kg/min) selected as

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the most consistent and interpretable dosing metric. ¶Estimated by averaging the mean differences between the high-target and control groups at all 19 time points (0–72 hours) provided in the article's Table E2 for the intention-to-treat population.

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Risk of bias analysis:

We evaluated the risk of bias (RoB)[13] for the primary mortality outcome in the four included randomised controlled trials using the Cochrane RoB 2.0 tool. The 65 Trial was judged to have an overall low risk of bias. The SEPSISPAM and OPTPRESS trials were rated as having some concerns. For SEPSISPAM, this primarily reflected deviations from the intended intervention, characterised by frequent and imbalanced clinician overrides of the high-target strategy. For OPTPRESS, the primary concern was the potential for overestimation of the effect size following early termination for ineffectiveness; its protocolised early vasopressin use is a feature affecting external validity but not a direct source of bias in the RoB2 framework.

The OVATION pilot trial was also rated as having some concerns, due to issues with adherence to the intervention and the selection of the reported result, the latter evidenced by the absence of pre-registration and some data available only via secondary publications from the same authors[23]. Although the nominal MAP separation was approximately 9 mmHg, effective separation was reduced by high crossovers (27%) and prolonged time outside the assigned targets (≥38% time), attenuating the trial's internal validity.

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Across all trials, the unblinded design was not considered a major source of bias for the objective outcome of all-cause mortality. Protocol adherence was sufficient to demonstrate a meaningful physiological-pharmacological separation between groups, as confirmed by consistently higher vasopressor exposure in the higher-target arms. Its feasibility purpose contextualises the limitations of the OVATION trial, and its minimal weight in any pooled analysis mitigates its impact on the overall body of evidence.

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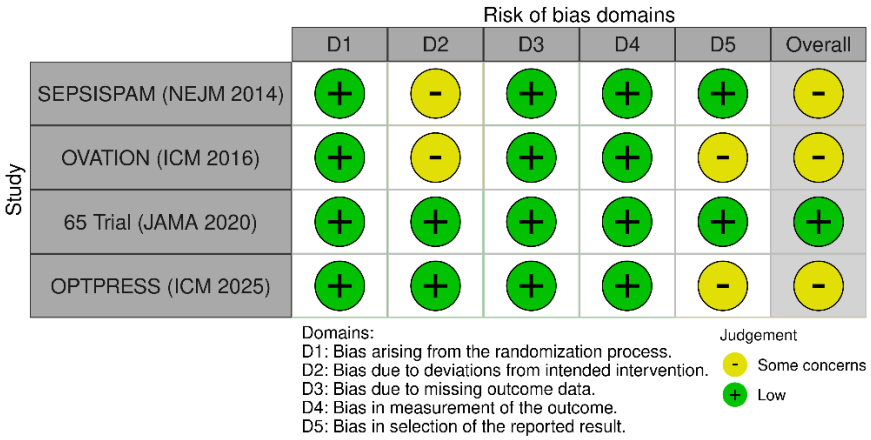
297 Table 2: Risk of bias.



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299 Trial sequential analysis:

300 Trial sequential analysis revealed that the cumulative Z-curve crossed the
301 conventional significance boundary but not the adjusted boundary, indicating that
302 while the point estimates are consistent and statistically significant under the
303 conventional threshold, further research could still be informative (Figure 2).

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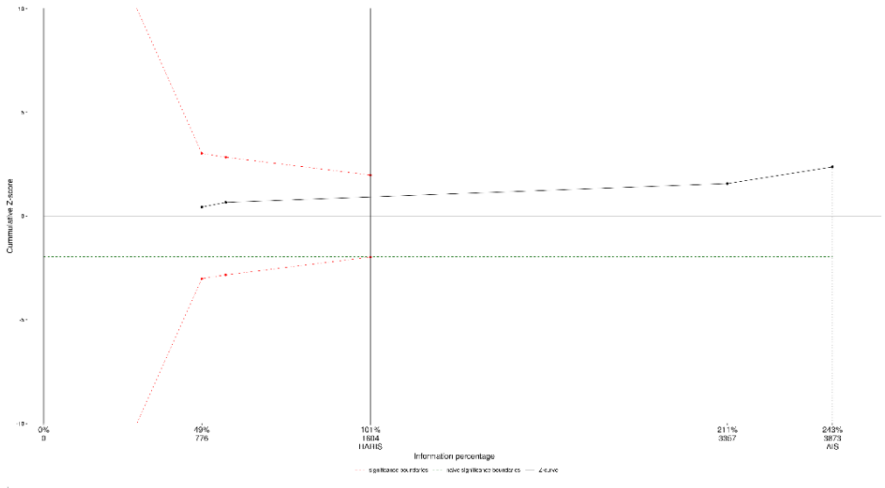
305 Figure 2: Z score plot.



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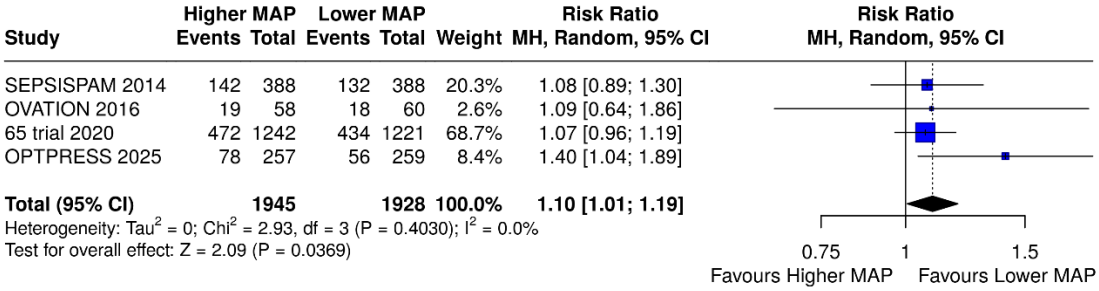
Footnote: AIS = actual information size, HARIS = heterogeneity adjusted recommended information size.

Primary outcome: all-cause mortality

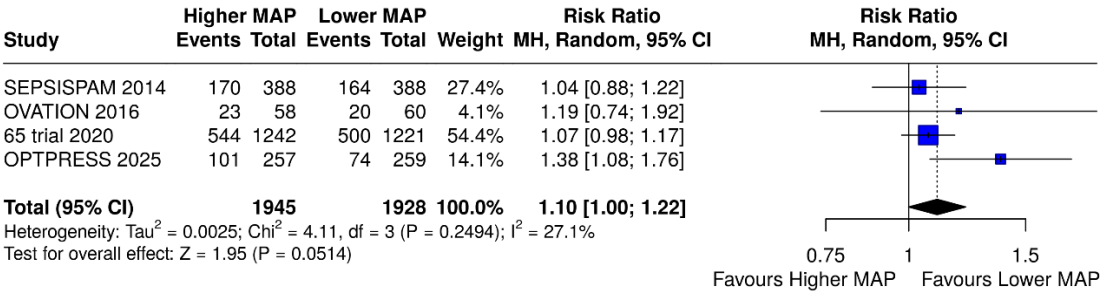
A higher MAP target was associated with increased mortality at 28 days by 10% (RR 1.10, 95% CI 1.01–1.19, P=0.037), with minimal heterogeneity (I^2 = 0%) (Figure 3). This signal of harm persisted at 90 days, with a trend toward a 10% increase in mortality risk (RR 1.10, 95% CI 1.00–1.22; P = 0.051) (Figure 4).

Figure 3: Pooled 28-day mortality.


Higher MAP
Lower MAP
Risk Ratio
Risk Ratio
Study
Events Total Events Total Weight MH, Random, 95% CI
MH, Random, 95% CI
SEPSISPAM 2014 142 388 132 388 20.3% 1.08 [0.89; 1.30]
OVATION 2016 19 58 18 60 2.6% 1.09 [0.64; 1.86]
65 trial 2020 472 1242 434 1221 68.7% 1.07 [0.96; 1.19]
OPTPRESS 2025 78 257 56 259 8.4% 1.40 [1.04; 1.89]
Total (95% CI) 1945 1928 100.0% 1.10 [1.01; 1.19]
Heterogeneity: Tau² = 0; Chi² = 2.93, df = 3 (P = 0.4030); I² = 0.0%
Test for overall effect: Z = 2.09 (P = 0.0369)
0.75
1
1.5
Favours Higher MAP
Favours Lower MAP

Footnote: OVATION[21] reported an overall mortality of 30% at 28 days and 31% in-hospital. However, the breakdown between the treatment arms was only directly provided for hospital mortality, which was used here as the most proximal outcome available.

Figure 4: Pooled 90-day mortality.


Higher MAP
Lower MAP
Risk Ratio
Risk Ratio
Study
Events Total Events Total Weight MH, Random, 95% CI
MH, Random, 95% CI
SEPSISPAM 2014 170 388 164 388 27.4% 1.04 [0.88; 1.22]
OVATION 2016 23 58 20 60 4.1% 1.19 [0.74; 1.92]
65 trial 2020 544 1242 500 1221 54.4% 1.07 [0.98; 1.17]
OPTPRESS 2025 101 257 74 259 14.1% 1.38 [1.08; 1.76]
Total (95% CI) 1945 1928 100.0% 1.10 [1.00; 1.22]
Heterogeneity: Tau² = 0.0025; Chi² = 4.11, df = 3 (P = 0.2494); I² = 27.1%
Test for overall effect: Z = 1.95 (P = 0.0514)
0.75
1
1.5
Favours Higher MAP
Favours Lower MAP

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Subgroup analyses:

Subgroup analyses for 28-day mortality were precluded by a lack of disaggregated data. At the 90-day endpoint, however, analyses by age suggested a potential association between higher MAP targets and increased mortality in patients aged ≥65 years (RR 1.17, 95% CI 1.02–1.34), but not in those <65 years (RR 0.92, 95% CI 0.70–1.22). See Figure 5. Similarly, in patients with septic shock, higher MAP targets were associated with a non-significant increase in mortality (RR 1.12, 95% CI 0.99–1.27; P = 0.06) (Figure 6). Among patients with chronic hypertension, the point estimate also suggested a potential harm (RR 1.11, 95% CI 0.98–1.25), a trend that was consistent in non-hypertensive patients (RR 1.16, 95% CI 0.94–1.43) (Figure 7).

When the credibility of these subgroup effects was formally assessed using the ICEMAN[16] tool, none met the criteria for high credibility. Although the hypotheses for age, chronic hypertension, and septic shock were pre-specified and biologically plausible, the statistical tests for interaction were non-significant, and the effect sizes were similar across subgroups. This pattern indicates that these patient characteristics are unlikely to be genuine effect modifiers of the relationship between MAP targets and mortality. This is particularly evident for the age subgroup, where the non-significant interaction test (P = 0.13) and severe underpowering in the younger cohort suggest that the observed difference is more likely due to random error than to a true effect modification.

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Figure 5: Pooled 90-day mortality across age subgroups.

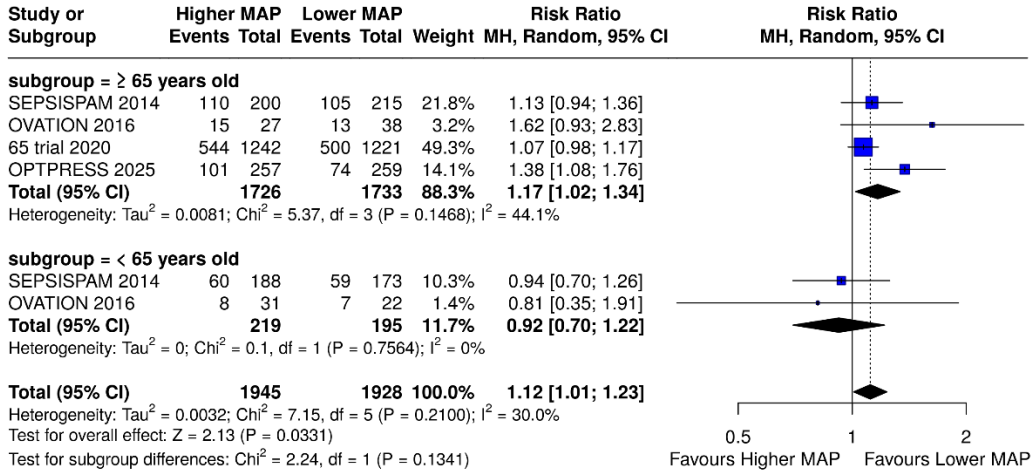
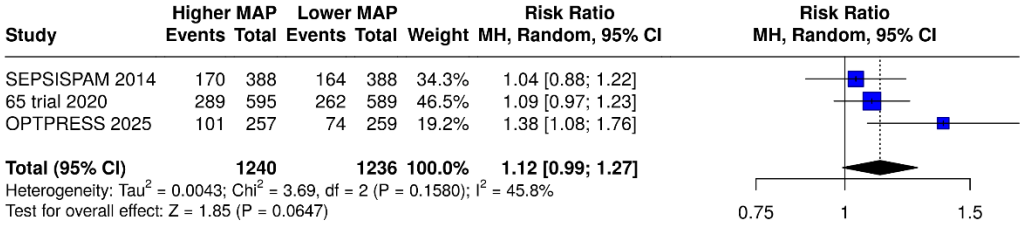

Study or Subgroup
Higher MAP Events Total
Lower MAP Events Total
Weight
Risk Ratio MH, Random, 95% CI
Risk Ratio MH, Random, 95% CI
subgroup = ≥ 65 years old
SEPSISPAM 2014 110 200 105 215 21.8% 1.13 [0.94; 1.36]
OVATION 2016 15 27 13 38 3.2% 1.62 [0.93; 2.83]
65 trial 2020 544 1242 500 1221 49.3% 1.07 [0.98; 1.17]
OPTPRESS 2025 101 257 74 259 14.1% 1.38 [1.08; 1.76]
Total (95% CI) 1726 1733 88.3% 1.17 [1.02; 1.34]
Heterogeneity: Tau² = 0.0081; Chi² = 5.37, df = 3 (P = 0.1468); I² = 44.1%
subgroup = < 65 years old
SEPSISPAM 2014 60 188 59 173 10.3% 0.94 [0.70; 1.26]
OVATION 2016 8 31 7 22 1.4% 0.81 [0.35; 1.91]
Total (95% CI) 219 195 11.7% 0.92 [0.70; 1.22]
Heterogeneity: Tau² = 0; Chi² = 0.1, df = 1 (P = 0.7564); I² = 0%
Total (95% CI) 1945 1928 100.0% 1.12 [1.01; 1.23]
Heterogeneity: Tau² = 0.0032; Chi² = 7.15, df = 5 (P = 0.2100); I² = 30.0%
Test for overall effect: Z = 2.13 (P = 0.0331)
Test for subgroup differences: Chi² = 2.24, df = 1 (P = 0.1341)
0.5
1
2
Favours Higher MAP
Favours Lower MAP

Figure 6: Pooled 90-day mortality in septic shock patients.


Study
Higher MAP Events Total
Lower MAP Events Total
Weight
Risk Ratio MH, Random, 95% CI
Risk Ratio MH, Random, 95% CI
SEPSISPAM 2014 170 388 164 388 34.3% 1.04 [0.88; 1.22]
65 trial 2020 289 595 262 589 46.5% 1.09 [0.97; 1.23]
OPTPRESS 2025 101 257 74 259 19.2% 1.38 [1.08; 1.76]
Total (95% CI) 1240 1236 100.0% 1.12 [0.99; 1.27]
Heterogeneity: Tau² = 0.0043; Chi² = 3.69, df = 2 (P = 0.1580); I² = 45.8%
Test for overall effect: Z = 1.85 (P = 0.0647)
0.75
1
1.5

Note: OVATION did not provide a breakdown by aetiology.

Figure 7: Pooled 90-day mortality by chronic hypertension status.

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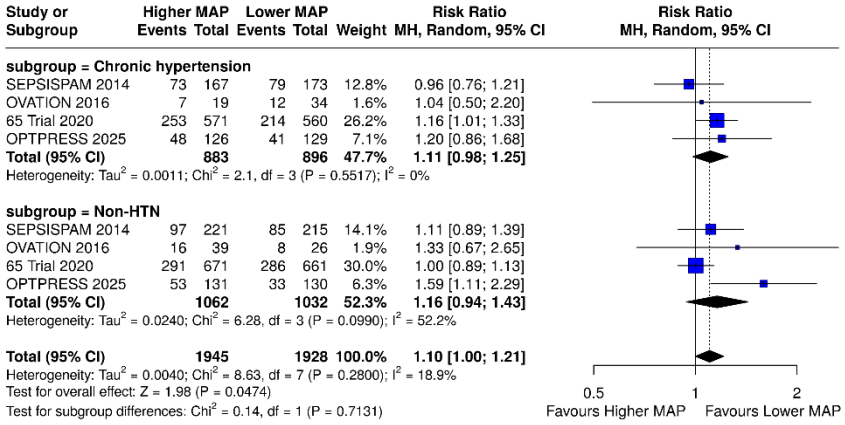
Study or Subgroup
Higher MAP Events Total
Lower MAP Events Total
Weight
Risk Ratio MH, Random, 95% CI
Risk Ratio MH, Random, 95% CI
subgroup = Chronic hypertension
SEPSISPAM 2014 73 167 79 173 12.8% 0.96 [0.76; 1.21]
OVATION 2016 7 19 12 34 1.6% 1.04 [0.50; 2.20]
65 Trial 2020 253 571 214 560 26.2% 1.16 [1.01; 1.33]
OPTPRESS 2025 48 126 41 129 7.1% 1.20 [0.86; 1.68]
Total (95% CI) 883 896 47.7% 1.11 [0.98; 1.25]
Heterogeneity: Tau² = 0.0011; Chi² = 2.1, df = 3 (P = 0.5517); I² = 0%
subgroup = Non-HTN
SEPSISPAM 2014 97 221 85 215 14.1% 1.11 [0.89; 1.39]
OVATION 2016 16 39 8 26 1.9% 1.33 [0.67; 2.65]
65 Trial 2020 291 671 286 661 30.0% 1.00 [0.89; 1.13]
OPTPRESS 2025 53 131 33 130 6.3% 1.59 [1.11; 2.29]
Total (95% CI) 1062 1032 52.3% 1.16 [0.94; 1.43]
Heterogeneity: Tau² = 0.0240; Chi² = 6.28, df = 3 (P = 0.0990); I² = 52.2%
Total (95% CI) 1945 1928 100.0% 1.10 [1.00; 1.21]
Heterogeneity: Tau² = 0.0040; Chi² = 8.63, df = 7 (P = 0.2800); I² = 18.9%
Test for overall effect: Z = 1.98 (P = 0.0474)
Test for subgroup differences: Chi² = 0.14, df = 1 (P = 0.7131)
0.5
1
2
Favours Higher MAP
Favours Lower MAP

Secondary outcomes: renal outcomes.

Higher MAP targets significantly decreased the overall number of RRT-free days (mean difference -1.64, 95% CI -3.05 to -0.23), with a similar effect on the chronic hypertensive subgroup. See Figure 8. The RRT-use data, presented in eFigure 1 (see Supplement 3), and discussion about the renal results, including competing-risk considerations, are further explored in Supplement 3.

Secondary outcomes: adverse reactions.

Higher MAP targets were associated with an increased risk of cardiac arrhythmias (RR, 1.32; 95% CI, 1.01–1.72), particularly supraventricular arrhythmias (RR, 1.71; 95% CI, 1.12–2.61). No significant differences were observed for ventricular arrhythmias, myocardial injury, bleeding, gastrointestinal ischaemia, or limb ischaemia. See Table 3.

Figure 8: RRT-free days by chronic hypertensive status.

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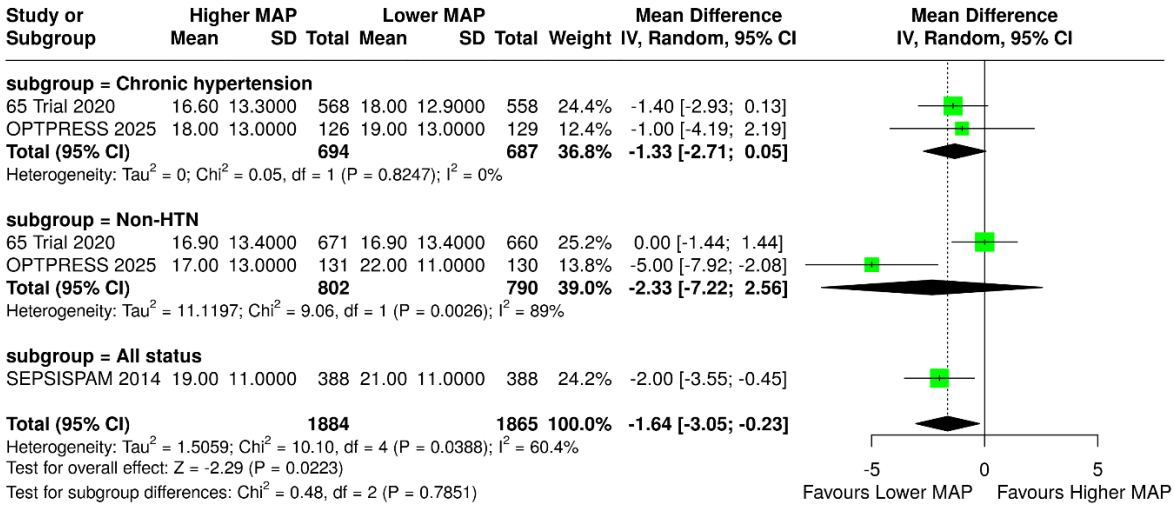
Study or Subgroup
Higher MAP Mean SD Total
Lower MAP Mean SD Total
Weight
Mean Difference IV, Random, 95% CI
Mean Difference IV, Random, 95% CI
subgroup = Chronic hypertension
65 Trial 2020 16.60 13.3000 568 18.00 12.9000 558 24.4% -1.40 [-2.93; 0.13]
OPTPRESS 2025 18.00 13.0000 126 19.00 13.0000 129 12.4% -1.00 [-4.19; 2.19]
Total (95% CI) 694 687 36.8% -1.33 [-2.71; 0.05]
Heterogeneity: Tau² = 0; Chi² = 0.05, df = 1 (P = 0.8247); I² = 0%
subgroup = Non-HTN
65 Trial 2020 16.90 13.4000 671 16.90 13.4000 660 25.2% 0.00 [-1.44; 1.44]
OPTPRESS 2025 17.00 13.0000 131 22.00 11.0000 130 13.8% -5.00 [-7.92; -2.08]
Total (95% CI) 802 790 39.0% -2.33 [-7.22; 2.56]
Heterogeneity: Tau² = 11.1197; Chi² = 9.06, df = 1 (P = 0.0026); I² = 89%
subgroup = All status
SEPSISPAM 2014 19.00 11.0000 388 21.00 11.0000 388 24.2% -2.00 [-3.55; -0.45]
Total (95% CI) 1884 1865 100.0% -1.64 [-3.05; -0.23]
Heterogeneity: Tau² = 1.5059; Chi² = 10.10, df = 4 (P = 0.0388); I² = 60.4%
Test for overall effect: Z = -2.29 (P = 0.0223)
Test for subgroup differences: Chi² = 0.48, df = 2 (P = 0.7851)
-5
0
5
Favours Lower MAP
Favours Higher MAP

Footnote: RRT-free days are defined as days alive and free of renal support within the first 28 days after randomisation, with zero days assigned to nonsurvivors. The SEPSISPAM[6] did not provide a breakdown by hypertensive status.

Table 3: Secondary outcome: selected complications from higher vs lower MAP targets.

Complication		Higher MAP (events/total)	Lower MAP (events/total)	Risk Ratio (95% CI)
Cardiac arrhythmia		121/2003	91/1989	1.32 [1.01, 1.72]
	Supraventricular	57/1746	33/1730	1.71 [1.12, 2.61]
	Ventricular	31/1746	30/1730	1.02 [0.62, 1.68]
Myocardial injury		28/1746	21/1730	1.32 [0.75, 2.32]
Bleeding		48/2003	56/1989	0.85 [0.58, 1.25]
GI ischaemia		24/1746	20/1730	1.19 [0.66, 2.14]
Limb/digital ischaemia		13/1746	16/1730	0.81 [0.39, 1.67]

Sensitivity analysis

Exclusion of the OVATION[21] trial: To evaluate the stability of the findings and the influence of small-study effects and the different proximal endpoints, a sensitivity analysis was conducted, excluding the OVATION pilot trial from the pooled estimates. In this scenario, the pooled risk ratio (RR) for 28-day mortality

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comparing higher versus lower MAP targets was 1.10 (95% CI 1.00–1.20). The 90-day mortality yielded a similar point estimate of 1.11 (95% CI 0.98–1.25).

Exclusion of the 65[7] trial: Given the previously discussed singularity with the treatment arms in the 65 trial, its exclusion from the pooling results was performed to confirm the robustness of our findings. The 28-day mortality and the 90-day mortality in this alternative analysis yielded RRs of 1.17 (95% CI 0.96--1.43) and 1.17 (95% CI 0.95--1.44), respectively.

Inclusion of the TARGET-C[22] trial: The TARGET-C (n=150) was a single-country multicentre RCT in patients with cirrhosis and septic shock that compared high (80–85 mmHg) versus standard (60–65 mmHg) MAP targets and reported no mortality benefit at 28 days (41.5% vs. 42.9%, P = 0.88). Its incorporation into the 28-day mortality pooled analysis minimally reinforced the confidence interval towards a detrimental effect of higher MAP targets. There were no 90-day mortality data available.

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Bayesian analysis:

The primary results of the Bayesian hierarchical meta-analysis are summarised in eTable 1 (28-day mortality) and eTable 2 (90-day mortality) (see Supplement 2). Model diagnostics, including heterogeneity estimates (τ) and prediction intervals, are provided in eTable 3-eTable 5; while the visual posterior predictive checks, demonstrating excellent model calibration, are presented in eFigure 1 (28-day mortality) and eFigure 2 (90-day mortality) (see Supplement 2).

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28-day mortality — Under the primary weakly informative prior, the Bayesian hierarchical model estimated a median RR of 1.118 (95% Credible Interval [CrI] 1.003–1.257) for higher versus lower MAP targets, with a posterior probability of harm [RR > 1] of 97.8%. The alternative sceptical prior yielded a RR of 1.082 (95% CrI 0.990–1.200), with a P(RR>1) of 95.8%. All leave-one-out analyses retained a P(RR>1) of more than 84%, whereas the fixed-effect model showed the greatest certainty [RR 1.101, 95% CrI 1.011–1.201, P(RR>1) = 98.7%]. Between-study heterogeneity was modest but imprecise (τ = 0.133, 95% CrI 0.006–0.716). Correlation was not substantial (see Supplement 2 eTable 6). The 95% prediction interval for the study-specific risk ratio (PI) was 0.728–1.659.

90-day mortality — Under the primary weakly informative prior, the Bayesian hierarchical model estimated a median RR of 1.115 (95% CrI 1.013–1.240) for higher versus lower MAP targets, with a P(RR>1) of 98.7%. The alternative sceptical prior yielded a RR of 1.081 (95% CrI, 0.999–1.194) and a P(RR>1) of 97.3%. All leave-one-out analyses retained a P(RR>1) of more than 87%, whereas the fixed-effect model showed the greatest certainty [RR 1.096, 95% CrI 1.016–1.182, P(RR>1) = 99.1%]. Between-study heterogeneity was modest but imprecise (τ = 0.147, 95% CrI 0.007–0.745). Correlation was not substantial (see Supplement 2 eTable 6). The 95% PI was 0.628–2.399.

Grading of Recommendations, Assessment, Development, and Evaluation assessment:

The results of the GRADE evaluation are provided in Table 3. For both the 28-day and 90-day all-cause mortality outcomes, the meta-analysis of four randomised controlled trials (n=3,873) showed that the higher-MAP target intervention led to

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452 an increased risk (RR 1.10) with 95% confidence intervals of 1.01-1.19 and 1.10 to
453 1.20, respectively. The certainty of this evidence was assessed as moderate.

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Table 3: Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) assessment of the evidence certainty on mortality effects of Higher MAP vs Lower MAP target in vasodilatory shock.

Certainty assessment							Summary of findings				
							Study event rates (%)			Anticipated absolute effects	
Participants (studies) Follow-up	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall certainty of evidence	With Lower MAP target	With Higher MAP target	Relative effect (95% CI)	Risk with Lower MAP target	Risk difference with Higher MAP target
28-day mortality											
3873 (4 RCTs)	not serious	not serious	not serious	serious[a]	none[b]	⨁⨁⨁◯ Moderate[a,b]	640/1928 (33.2%)	711/1945 (36.6%)	**RR 1.10** (1.01 to 1.19)	640/1928 (33.2%)	**33 more per 1,000** (from 3 more to 63 more)
90-day mortality											
3873 (4 RCTs)	not serious	not serious	not serious	serious[a]	none[b]	⨁⨁⨁◯ Moderate[a,b]	758/1928 (39.3%)	838/1945 (43.1%)	**RR 1.10** (1.00 to 1.22)	758/1928 (39.3%)	**39 more per 1,000** (from 0 fewer to 86 more)

CI: confidence interval; **RR:** risk ratio

Explanations

a. Although both point estimates yield a 10% relative increase in mortality risk (RR 1.10), the 95% confidence interval for 28-day mortality (1.01 to 1.19) has a lower bound that touches the line of no effect, and the interval for 90-day mortality (1.00 to 1.22) includes the null value, indicating the true effect could be negligible.
b. The included trials were predominantly at low risk of bias, and statistical heterogeneity was negligible. The patient population and interventions directly addressed the research question. For publication bias, formal tests (e.g., Egger's regression, Funnel plot) were foregone as per our prospective protocol due to an insufficient number of studies (k<10), which renders them unreliable. Instead, a judgment that publication bias was unlikely is based on a comprehensive, multi-database search and screening of reference lists.

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Discussion

This updated meta-analysis of randomised controlled trials (RCTs) provides a comprehensive synthesis on the association of mean arterial pressure (MAP) targets in vasodilatory shock and mortality, integrating recent evidence from over 3,800 patients across four trials. The frequentist analysis demonstrated that a higher MAP target (75–85 mmHg) is associated with a statistically significant 10% increase in 28-day mortality and a similar trend toward harm at 90 days. Although subgroup analyses based on age, hypertension status, or septic shock aetiology were prespecified and based on plausible pathophysiology, the ICEMAN[16] assessment indicated low credibility for true effect modification.

Importantly, our results reinforce and substantially strengthen the harm signal from higher MAP targets observed in prior evidence. A pre-OPTPRESS individual-patient data Bayesian meta-analysis[10] yielded a 90-day risk ratio of 0.93 (95% CrI 0.76–1.07), favouring lower targets, with an 87% posterior probability of benefit. After incorporating the OPTPRESS[11] trial, which met predefined ineffectiveness criteria for early termination, our updated trial-level model yielded a 90-day risk ratio of 1.115 (95% CrI 1.013–1.240) with a 98.7% posterior probability of harm. Hence, this additional information shifts the evidence from suggestive to strongly supportive of harm with higher MAP targets, modestly improves precision, and increases granularity for prespecified subgroup and secondary-outcome analyses.

The overall finding of an increased propensity for death with higher MAP targets was consistent across both endpoints in the primary Bayesian model using a weakly informative prior (97.8% for 28-day mortality and 98.7% for 90-day mortality). Robustness was confirmed under sceptical priors (95.8% and 97.3%, respectively), fixed-effect modelling, and leave-one-out analyses, all of which retained a posterior probability of harm ≥ 84%.

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Crucially, while previous observational data suggested potential benefits from higher MAP targeting, this meta-analysis unequivocally discourages its universal use. This aligns with prior systematic reviews[8,9], which reported no statistically robust interaction for age, hypertension status, or septic shock aetiology. The consistent signal of harm across multiple analytical frameworks strongly suggests that the adverse effects of targeting a higher MAP are not merely statistical but physiological, possibly driven by the inherent toxicity of the vasopressors required to achieve these targets.

Vasopressors can exert direct organ toxicity, including myocardial injury, arrhythmias, and metabolic disturbances.[24] Our safety analysis highlighted elevated arrhythmia risk (RR 1.32, 95% CI 1.01–1.72), particularly supraventricular events (RR 1.71, 95% CI 1.12–2.61), with increased MAP targeting. Additionally, catecholamines exacerbate oxidative stress and mitochondrial dysfunction[25], may have an immunosuppressive effect[26], and promote endothelial damage and coagulopathy.[27] Observational data have suggested an association between increasing noradrenaline-equivalent dosing and mortality, even after adjustment for confounders such as illness severity and fluid status[28], which seems to be dose-dependent.[29] This pathophysiological explanation for our pooled results finds compelling support in a recent post-hoc analysis of the SEPSISPAM trial.[30] In this analysis, which employed advanced causal inference methods to test for heterogeneity of treatment effect, no baseline patient characteristic, including chronic hypertension, identified a subgroup that benefited from a higher MAP target. Importantly, the data revealed that the harm was likely mediated through the physiological consequences of the intervention itself: mortality increases when achieving a higher target requires large norepinephrine doses or fails to resolve skin mottling within 24 hours. These findings provide a plausible mechanistic explanation for our pooled results, confirming that universally targeting a higher

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MAP is not merely ineffective but actively detrimental, and challenge the long-held belief that certain patient phenotypes warrant a higher MAP.

Despite international guidelines endorsing a MAP ≥65 mmHg[2], real-world practice frequently far exceeds this threshold[3]. Our findings challenge this practice, demonstrating that routinely targeting a MAP 80±5 mmHg may increase mortality, even in subgroups historically presumed to benefit from higher pressures (e.g., chronic hypertension).

Our study has several notable strengths that increase the robustness and clinical relevance of its findings. First, our methodology was driven by a prospectively registered protocol (PROSPERO CRD420251087844), ensuring transparency and minimising reporting bias. Second, this meta-analysis incorporates well-designed contemporary trials, encompassing a substantial patient cohort (n = 3,873), which contributes to statistical power. A significant strength lies in our dual analytical approach, which employs both frequentist and Bayesian hierarchical meta-analyses. The consistency of the results across these different statistical frameworks reinforces the credibility of our conclusions. Furthermore, by focusing exclusively on vasodilatory shock, we achieve a higher degree of homogeneity in the underlying shock phenotype, minimising confounding due to diverse aetiologies. This underpins the decision to limit the TARGET-C[22] data to the sensitivity analysis.

Despite these strengths, our study has limitations, the most significant being the limited number of trials (k = 4). This affects interpretation in three ways. First, heterogeneity is weakly identified: the between-study SD is imprecise (τ = 0.13–0.14; Supplement S2 eTable 5), so we de-emphasised I^2 in favour of τ and prediction intervals. Second, the pooled harmful effect was stable across Bayesian and frequentist random-effects models, including leave-one-out and sensitivity

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analyses (τ-prior variants and alternative heterogeneity estimators). Third, generalisability is context-dependent: the 95% prediction intervals on the RR scale are wide (28-day: 0.72–1.65; 90-day: 0.62–2.39), indicating possible variation across settings. Despite this, the effect consistently pointed toward harm, arguing against the universal application of higher MAP targets.

We observed heterogeneity in the definitions of 'higher' and 'lower' MAP thresholds across trials (e.g., the usual-care arm in the 65 Trial allowed a broader MAP range). Variations in intervention duration and vasopressor strategies, such as early vasopressin in OPTPRESS, could influence outcomes and interact with MAP targets. The timing of endpoint ascertainment also varied across studies, which, while accounted for in our analyses, represents another source of heterogeneity. Although most trials enrolled patients with septic shock, the 65 Trial and OVATION included broader vasodilatory shock, introducing clinical heterogeneity. The open-label design introduces potential performance bias, though the objective primary outcome (all-cause mortality) mitigates its impact. Finally, under sceptical priors, credible intervals marginally include the null, indicating residual uncertainty despite high posterior probabilities of harm.

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A key limitation of this meta-analysis is the dominant contribution of the 65 Trial. It contributed to 64% of the total sample size, resulting in statistical weights ranging from 46% to 68% across different endpoints and models, exerting a dominant influence on the pooled effect estimates. Notably, while the 65[7] trial compared a permissive hypotension strategy (MAP 60–65 mmHg) to usual care, the achieved MAP separation (66.7 vs. 72.6 mmHg) and nearly 50% increase in the noradrenaline-equivalent dose (NE) across the arms (17.7 vs. 26.4 mg) closely mirrored other trials. For example, in OPTPRESS[11], a 5 mmHg MAP difference (77.6 vs. 72.6 mmHg) required a 62% increase in the vasopressor dose (15.6 vs 9.6 mg over 72 h), and in SEPSISPAM[6], the high-MAP arm required twice more NE.

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Therefore, the physiological and pharmacological gradients in the 65 trial are consistent with the experimental contrasts in other trials, justifying its inclusion in the pooled results. Furthermore, when pooled with the three other trials, it decreases the measured heterogeneity (I^2 consistently < 25% in this and previous meta-analyses). This statistical similarity supports the idea that the treatment effect it estimates is comparable in magnitude and direction to that of the other trials. Sensitivity analyses, including leave-one-out models, were therefore conducted to assess the robustness of the findings when this dominant trial was excluded.

Another important limitation of our meta-analysis is the inability to explore the heterogeneity of treatment effects. The available trial-level data do not allow for detailed subgroup analyses on the basis of individual patient characteristics. It is plausible that certain patient phenotypes may influence the physiological and clinical response to differing MAP targets. However, the included RCTs and current meta-analyses have only examined the effects of uniformly applying high- or low-MAP targets at the population level. This approach may obscure differential effects across subpopulations, and it precludes tailored blood pressure strategies based on individual risk–benefit profiles.

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Individualised hemodynamic management and the use of tissue-perfusion endpoint (e.g., capillary refill time[31], capillary blood flow, renal resistive index) rather than fixed MAP thresholds should be prioritised in future research. Trials, such as the React-SHOCK pilot[32], demonstrate the feasibility of personalised targets in a population with shock of mixed aetiologies. The future results of the React-SHOCK multicentre RCT (NCT05850962), which is currently randomising shocked patients to either a blood pressure target similar to their pre-existing blood pressure or standard care, will be pivotal in determining whether this personalisation materialises in better patient outcomes.

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In conclusion, a uniform application of higher MAP targets (80±5 mmHg) in patients with vasodilatory shock is associated with increased mortality, with moderate certainty. The number needed to harm was 33 at 28 days and 39 at 90 days, underscoring the clinical significance of our findings. Given the high global incidence of vasodilatory shock, this suggests that adhering to lower MAP targets could prevent a substantial number of deaths, reinforcing the critical need for judicious vasopressor use to balance hemodynamic support with the risk of adverse effects. Transitioning from fixed pressure targets to personalised or perfusion-guided approaches represents the next frontier in critical care haemodynamic research.[33]

Declarations

Ethics approval and consent to participate:

Not applicable.

Consent for publication:

Not applicable.

Availability of supporting data:

No new primary data were generated. The Bayesian analysis code is provided in the supplementary materials. The complete search strategy is detailed in the Methods section and the preregistered protocol (PROSPERO CRD420251087844). The dataset extracted from the included studies is available from the corresponding author upon reasonable request.

Competing interests:

The authors declare that they have no competing interests.

Funding:

Not applicable.

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Authors' contributions:

H.M. conceived the study. H.M., K.D., and N.K. were responsible for the study design. H.M. and J.K. performed the literature search, study selection, data extraction, and the risk of bias and GRADE assessments. All authors contributed to the interpretation of the results, critically revised the manuscript for important intellectual content, and approved the final version for publication.

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